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Maternal education has significant influence on progression in multiple sclerosis

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ABSTRACT

Objective: The identification of potential risk factors for disease severity is of great importance in the treatment of multiple sclerosis. The influence of socioeconomic status on progression in multiple sclerosis (MS) is sparsely investigated. Our aim was to investigate how socioeconomic status in adolescence influences disease progression in later life.

Methods: A total of 1598 patients with multiple sclerosis from a well-defined population in Norway were included. Detailed information on disease progression, measured by expanded disability status scale (EDSS) and multiple sclerosis severity score (MSSS), were combined with data on socioeconomic factors. We used residency and parental level of education at patients' age 16 and exposure to second-hand smoking as a measure of socioeconomic status in adolescence, adjusting for the same variables as well as use of disease modifying treatments at prevalence date 01.01.18.

Results: High maternal level of education at patients' age 16 was significantly associated with less pronounced disease progression measured by MSSS (β-coefficient -0.58, p = 0.015), younger age and lower EDSS at disease onset, and shorter time from onset to diagnosis. No significant associations were found for paternal education level and MSSS. The use of any disease modifying treatment before prevalence date was significantly associated with disease progression (β-coefficient -0.49, p=0.004), while residence, current and second-hand smoking were not.

Conclusion: This study on a population-based, real-world cohort shows that the parental level of education has a significant impact on a timely diagnosis of MS. In addition to disease modifying treatment, maternal level of education also had an impact on disease progression in later life.

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease with secondary neurodegeneration that causes significant disability in young people over time (Collaborators GBDMS 2019). The national prevalence in Norway was 203/100 000 in 2012, which is among the highest in the world (Berg-Hansen et al., 2014), and recent data suggest a marked increase (Flemmen et al., 2020). There is increasing evidence for an association between socioeconomic status (SES), defined as the standing of a person measured by a combination of economic and social factors in relation to others, and the risk for MS (FB et al., 2015). There is substantial evidence that individuals with low SES have poorer health conditions in general, compared to those with higher SES (Mackenbach et al., 2018). This is also seen in welfare states traditionally marked by

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commitment to social equality, such as the Nordic countries (Lahelma et al., 2001).

MS occurs with greater frequency in high-income nations (Buchter et al., 2012). Some studies have concluded that there is a tendency for higher susceptibility to MS in households of greater affluence (Montgomery et al., 2004; Kurtzke and Page, 1997). The evidence in a multinational review is however inconsistent, and some studies find no social gradient, or even the opposite (Goulden et al., 2015). Some studies have examined the association between childhood SES and the risk of MS. In a Danish cohort, researchers found reduced rates of MS later in life if the maternal level of education was greater than secondary school when the offspring was aged 15 (Nielsen et al., 2013). A multinational study from 2016 did not find a consistent association between parental SES and MS risk in Norway, Canada and Italy (Goulden et al., 2016).

The association of SES with disease progression has been examined to a much smaller extent. Recent studies from Canada, UK and France show that there is an association between socioeconomic deprivation and a higher risk of disability progression, measured by time from onset to expanded disability status scale (EDSS) 4 and 6 (Harding et al., 2019; Calocer et al., 2020). A Flemish study showed that self-reported high levels of education prevented disability progression (D'Hooghe et al., 2016). Other studies have suggested variations within countries, with some evidence that place of residence, age, sex and ethnicity may influence disease progression in MS patients (Roddam et al., 2019).

When addressing socioeconomic factors and health, it is important to keep in mind that health-related behavior, such as smoking, is influenced by SES (Allen et al., 2017). Those who achieve a higher level of educational attainment are more likely to engage in healthy behaviors (van Oort et al., 2004). Smoking is an established risk factor for MS, and there is evidence of a causal relationship between smoking and subsequent development and progression of MS. Results on the effect of second-hand smoking are, however, mixed, and none of these are adjusted for SES (Degelman and Herman, 2017).

The aim of this study was to investigate how SES in adolescence influences disease progression later in life. Since the onset of MS usually occurs at a young age, and the disease can impair the patient's cognitive performance for years before the onset of symptoms (Cortese et al., 2016), the patient's own level of education may not be an accurate measure of SES. We have chosen the parental level of education as a more appropriate measure for the influence of education. To our knowledge, this has not been studied before.

2. Material and methods

2.1. Population

This study is part of an ongoing study on all MS patients in the counties Buskerud and Telemark, as well as the majority of patients in Oslo (BOT-MS, n=3965) (Simonsen et al., 2020). These counties comprise a population of 1.17 million people in South-Eastern Norway. The regional ethics committee of South-East Norway (REK 2015/670) has approved the project. All patients provided written, informed consent.

2.2. Methods

All patients with a definite diagnosis of MS according to the prevailing diagnostic criteria (Thompson et al., 2018) were registered, as described by Simonsen et al. (2020) Data were recorded prospectively, but retrospectively retrieved. Data collection for this study was terminated 01.01.2018, defined as prevalence date. For each patient, we collected time of onset and diagnosis, disease subtype at diagnosis, any disease modifying treatments (DMT) and disability as measured EDSS (Kurtzke, 1983). The EDSS assessments were collected at as many time points as possible by three Neurostatus certified neurologists (D'Souza et al., 2017). The multiple sclerosis severity score (MSSS) adds the element of disease duration to the EDSS, and is designed to provide a measure of disease severity (Roxburgh et al., 2005). We calculated the MSSS for each individual using the duration of MS from time of onset and the EDSS score nearest to prevalence date. We classified subtypes of MS as primary progressive (PP), secondary progressive (SP) or relapsing-remitting (RR), the latter included those initially registered with a clinically isolated syndrome (CIS), later verified as definite MS. In some sub analyses, we divided the population by diagnosis before and after 2006, the year the first high efficacy DMT, natalizumab, was introduced (Polman et al., 2006). We have further sub-grouped DMTs into moderate efficacy DMTs, including interferons, glatiramer acetate, teriflunomide and dimethyl-fumarate, and high efficacy DMTs, including natalizumab, fingolimod, alemtuzumab, rituximab and cladribine.

We have used three different measures for disease progression:

- **Change in EDSS the first five years after diagnosis**. For patients with more than five years since diagnosis, we have calculated change in EDSS in this period, using EDSS at the time of diagnosis and five years after diagnosis. If no EDSS score was available at year five (patient not seen by neurologist, presumably due to stable disease), the EDSS at the sixth (213/768) or seventh (81/768) year after diagnosis was used. An increase in EDSS by more than 2 points was labeled as *marked progression*, an increase by 1-2 points as *moderate progression*, a change by +/- 0.5 points as *stable disease* and, finally, a reduction in EDSS by 1 point or more as *improvement*.
- **Time to EDSS 6** was calculated in all patients who reached EDSS 6 by prevalence date.
- **The MSSS at prevalence date.** The MSSS is limited to 30 years after onset (Roxburgh et al., 2005). 251 patients were registered with onset of MS more than 30 years ago. For the individuals with 30-35 years since onset, we have registered the MSSS for year 30, but we have excluded the 147 patients with more than 35 years since onset. For patients with an unknown year of onset, we have not calculated an MSSS.

Statistics Norway has provided additional information, from annually performed censuses, on parental level of education and the municipality of residency at the patients' age 16, as well as the patients' own level of education and municipality at prevalence date. The level of education is divided into groups according to the total number of years in the Norwegian education system (0-9 years as primary, 10-12 years as secondary and 13 years or more as graduate level of education). We have also used the level of parental education combined, according to definitions given by Statistics Norway, labeled by the highest level of education both parents have achieved. The municipalities are recoded into six groups by the Centrality index. This index is developed by the Norwegian Government and measures how centrally the municipalities are located in terms of service functions and work places reachable for a resident within 90 minutes. Index 1 and 2 denotes the most central areas, index 5 and 6 the most rural areas (Høydahl, 2017). Statistic Norway has also provided data on level of education, smoking status and centrality indices for the general population in the three counties.

To add indicators of environmental factors and socioeconomic status, the patients provided information through a validated questionnaire (Unpublished, presented as e-poster at ECTRIMS 2019, P765 Socioeconomic factors as predictors for MS susceptibility and disease progression – validation of a new Norwegian questionnaire). In this study, we have only used information regarding smoking habits from this questionnaire.

2.3. Statistical analysis

We used IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) for statistical analysis. Data are presented as means ± standard deviation (SD), median with interquartile range (IQR), or

numbers and percentages depending on distribution. Cross tabulations were computed in order to investigate the relationship between different indicators of socioeconomic status and disease progression, given by change in EDSS the first five years after diagnosis. The chi-square test was used to detect associations between categorical variables. For the variables with significant associations, we performed a posthoc analysis, using stable disease as comparator for the two categories of progression of EDSS. We used independent sample t-test for normally distributed data to assess differences in continuous variables between groups. One-way ANOVA was used to compare means of age, time from onset to diagnosis and MSSS across subgroups. Kruskal-Wallis test was used to compare differences in EDSS across subgroups, as EDSS was skewed. To estimate time to EDSS 6 by socioeconomic variables during adolescence, we used the Kaplan-Meier method. Follow-up time was calculated as patient-years from time of onset until the date of EDSS 6, date of emigration or death, or prevalence date 01.01.2018, whichever occurred first. Univariable and multivariable linear regression models were used to analyze the impact of socioeconomic variables on progression by MSSS. Factors that are strongly associated are not included in multivariable analysis in order to avoid multicollinearity, using a Spearman correlation coefficient ≥ 0.7 as limit for multicollinearity. The final regression model was made by eliminating non-significant variables until all significant. The results from the regression analyses are presented as β coefficients, standard error of β (SE), p-values and explained variance (R^2). Heteroscedasticity and normality of residuals were examined and found to be satisfactory. All p-values were two-sided with a significance level of 5 %. We used the two-proportion z-test to compare the proportions of education, smoke and residence between background population and study population, using OpenEpi.com.

3. Results

All 2512 MS patients from the BOT registry who were still alive were invited to participate in the study. We received 1598 written consents and 1573 of these have completed the questionnaire.

Table 1 shows demographic data for the MS population at prevalence date 01.01.2018. The female patients (71%) are younger at both diagnosis and at prevalence date. The proportion of females remain stable for all variables, with three exceptions: Progressive subtype at diagnosis, the subgroup that reached EDSS 6 within prevalence date, and of persons with secondary school level of education in 2018. In these subgroups, the female proportion is lower (respectively 51 %, 64 % and 66 %, data not shown).

The study population was compared to the background population in the three counties of Buskerud, Oslo and Telemark using data from Statistics Norway 2018 (Fig. 1). The proportion living in centrality indices 1 - 4 is significantly lower in our MS population compared to the background population. There were more smokers among the MS patients than the in the background population, but the level of education is similar in the MS population and in the background population. Fig. 2 shows how the combined parental level of education is associated with a person's level of education, both for the MS population and for the general population in the three counties of Norway. The tendency to achieve higher levels of education when parents are educated more than 13 years is significantly more pronounced for MS patients compared to the general population.

3.1. Progression measured as change in EDSS five years after diagnosis

Table 2 shows the associations of socioeconomic factors during adolescence and change in EDSS the first five years after diagnosis. We found a significantly higher degree of disease progression in patients whose maternal level of education was limited to primary school. Patients whose mothers completed a graduate level of education, on the other hand, more often displayed improvement in EDSS by year five. The post hoc analysis showed that the association is significant when

Table 1
Demographics.

Total No.		1598
	Males (%)	469 (29.3)
	Females (%)	1129 (70.7)
Characteristics at 16 years of age	Centrality of municipality, n=1034	
	Centrality indices 1 and 2, %	40.7
	Centrality indices 3 and 4, %	45.2
	Centrality indices 5 and 6, %	14.2
	Paternal level of education, n=1374	
	Primary ≤ 9 years, %	30.7
	Secondary 10-12 years, %	46.1
	Graduate ≥ 13 years, %	23.1
	Maternal level of education, n=1404	
	Primary ≤ 9 years, %	35.3
	Secondary 10-12 years, %	48.7
	Graduate ≥ 13 years, %	16.0
	Exposed to second-hand smoke, n=1556, %	73.3
Characteristics at diagnosis	Mean age, years (SD), n=1535	39.5 (11.3)
	Mean age male, years (SD)	41.0 (10.9)
	Mean age female, years (SD)	38.9 (11.4)
	Mean time from onset to diagnosis, years (SD)	5.4 (7.0)
	Subtype MS, n=1528	
	RRMS, %	80.8
	PPMS, %	9.3
	SPMS, %	4.8
	Unknown, %	5.1
	Median EDSS (IQR)	2.5 (2.0-3.0)
Characteristics disease course	Mean change EDSS first five years after diagnosis (SD)	0.4 (1.5)
Characteristics at prevalence date 01.01.2018	Age, mean (SD), n=1598	52.5 (13.5)
	Mean age male, years (SD)	)53.9 (13.1)
	Mean age female, years (SD))	51.9 (13.6)
	Mean MSSS (SD)	3.34 (2.55)
	Reached EDSS 6, n=1362, %	24.8
	Treatment, n=1598	
	No treatment, %	40.1
	Moderate efficacy DMT, %	31.5
	High efficacy DMT, %	8.2
	Hospital responsible for follow-up, n=1298	
	University Hospital, %	25.8
	General Hospital, %	74.2
	Centrality of municipality, n=1595	
	Centrality indices 1 and 2, %	59.1
	Centrality indices 3 and 4, %	34.7
	Centrality indices 5 and 6, %	6.2
	Patient's level of education (n=1584)	
	Primary ≤ 9 years, %	17.5
	Secondary 10-12 years, %	38.5
	Graduate ≥ 13 years, %	44.0
	Current smokers, n=1563, %	27.1

n = numbers, SD = standard deviation, IQR = interquartile range, RRMS = relapsing remitting multiple sclerosis, PPMS = primary progressive multiple sclerosis, SPMS = secondary progressive multiple sclerosis, EDSS = Expanded Disability Status Scale, MSSS = Multiple Sclerosis Severity Score, DMT=disease modifying treatment

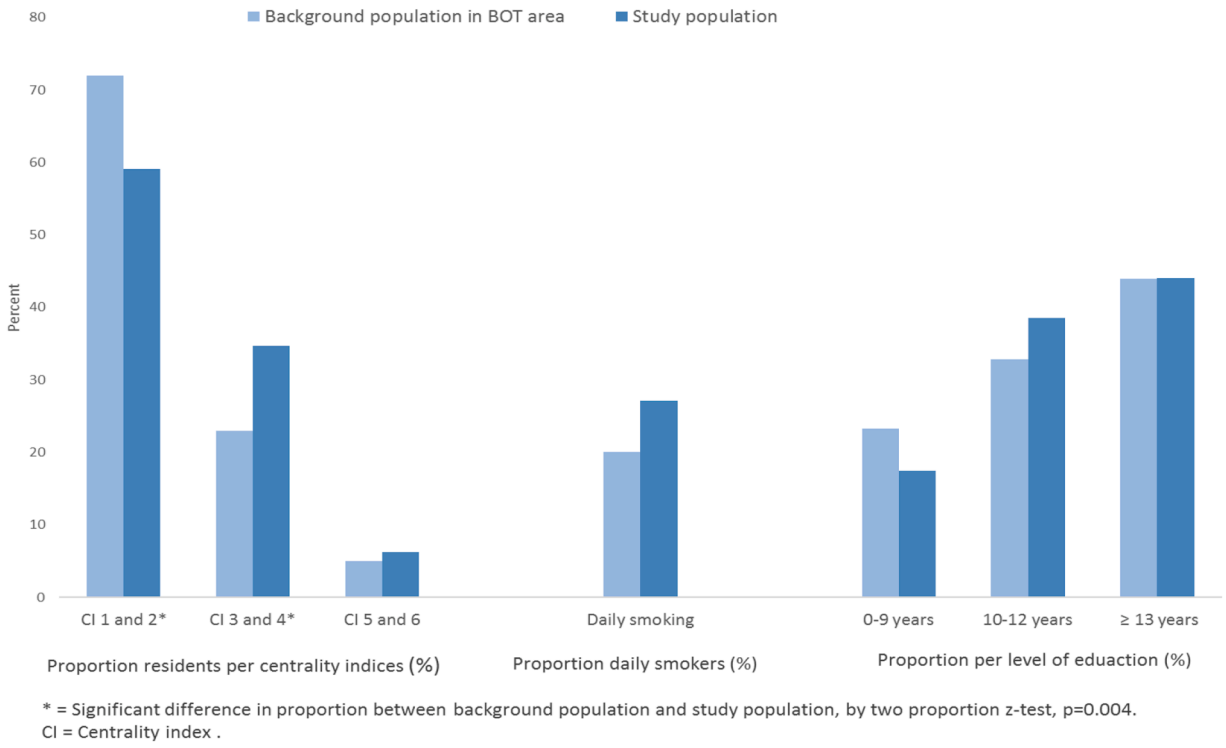

Fig. 1. Demographics 2018. Background population n= 925 483 (population 16 years and older in Buskerud, Oslo and Telemark, data from Statistics Norway) compared to study population n = 1598.

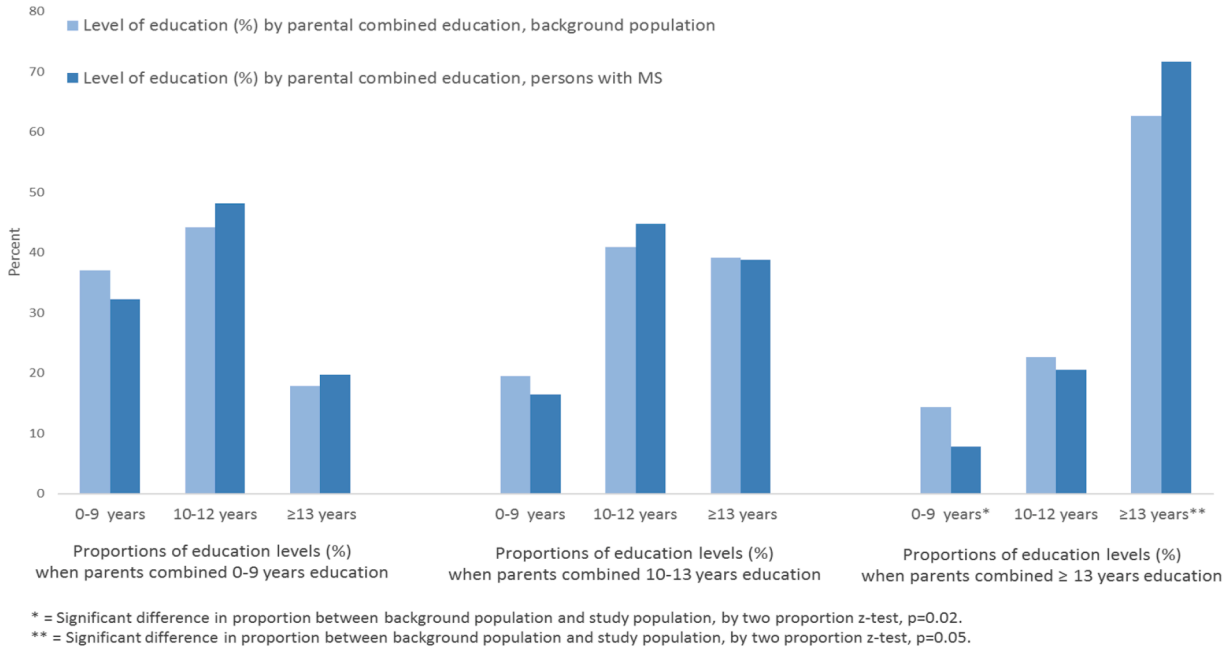

Fig. 2. Level of education by parents' combined level of education, 2018. Background population n= 925 483 (population 16 years and older in Buskerud, Oslo and Telemark, data from Statistics Norway) compared to study population n = 1598.

comparing stable disease to marked progression after five years of diagnosis. The association between the EDSS and the father's level of education shows a similar pattern, but does not reach significance. Patients who were diagnosed before year 2006 have a significantly more pronounced progression when compared with those diagnosed in 2006 and after. The post hoc analysis for this variable showed significant associations when comparing the category stable disease to both moderate and to marked progression. Neither living in a bigger city or in a rural area at age 16, nor exposure to second-hand smoking in the household reached significance with disease progression the first five years after diagnosis.

In Table 3, we present the grouped EDSS progression in the first five years against socioeconomic variables at prevalence date. The patient's own level of education and whether they were ever treated with DMTs are significantly associated with disease progression in the first five years after diagnosis.

Table 2
Association of socioeconomic factors in adolescence and time of diagnosis and change in EDSS year 0-5.

	Improvement (reduction of EDSS ≥1 point)	Stable disease (EDSS ±0.5 points)	Moderate progression (increase in EDSS 1-2 points	Marked progression (increase in EDSS ≥2 points)	Total
Total No. (%)	146 (22.1)	285 (43.1)	148 (22.4)	83 (12.5)	662 (100)
Sex					
Females (%)	103 (70.5)	210 (73.7)	103 (69.6)	51 (61.4)	467 (70.5)
Males (%)	43 (29.5)	75 (26.3)	56 (30.4)	32 (38.6)	195 (29.5)
p-value					*.193 (n. s.)*
Mean age at diagnosis, years (SD)	35.1 (10.2)	41.1 (11.6)	43.5 (10.6)	44.5 (11.0)	40.7 (11.4)
p-value					<.001
Paternal level of education at 16 years of age					
Primary ≤ 9 years (%)	43 (30.5)	78 (30.8)	51 (38.1)	30 (44.1)	202 (33.9)
Secondary 10-12 years (%)	62 (44.0)	118 (46.6)	62 (46.3)	31 (45.6)	273 (45.8)
Graduate ≥ 13 years (%)	36 (25.5)	57 (22.5)	21 (15.7)	7 (10.3)	121 (20.3)
p-value					*.077 (n. s.)*
Maternal level of education at 16 years of age					
Primary ≤ 9 years (%)	42 (30.0)	100 (38.8)	56 (41.8)	41 (58.6)	239 (39.7)
Secondary 10-12 years (%)	77 (55.0)	123 (47.7)	64 (47.8)	24 (34.3)	288 (47.8)
Graduate ≥ 13 years (%)	21 (15.0)	35 (13.6)	14 (10.4)	5 (7.1)	75 (12.5)
p-value				*	*.009*
Centrality of municipality at 16 years of age					
Centrality indices 1 and 2 (%)	57 (44.9)	71 (35.1)	30 (33.7)	18 (52.9)	176 (38.9)
Centrality indices 3 and 4 (%)	51 (40.2)	95 (47.0)	47 (52.8)	12 (35.3)	205 (45.4)
Centrality indices 5 and 6 (%)	19 (15.0)	36 (17.8)	12 (13.5)	4 (11.8)	71 (15.7)
p-value					*.224 (n. s.)*
Exposed to second-hand smoke					
Yes (%)	103 (72.0)	205 (74.3)	104 (73.2)	59 (75.6)	471 (73.7)
No (%)	40 (28.0)	71 (25.7)	38 (26.8)	19 (24.4)	168 (26.3)
p-value					*.936 (n. s.)*
Diagnosis before or after 2006					
Diagnosis ≤ 2006 (%)	53 (36.3)	114 (40.0)	76 (51.4)	55 (66.3)	298 (45.0)
Diagnosis > 2006 (%)	93 (63.7)	171 (60.0)	72 (48.6)	28 (33.7)	364 (55.0)
p-value			*	*	*<.001*

n= numbers, SD = standard deviation, n.s. =not significant
* = significant association at level < 0.05 in posthoc analysis when compared to category "stable disease"

3.2. Progression measured as time to EDSS 6

In total, 24 % (308/1304) had reached EDSS 6 by prevalence date, with a median time to EDSS 6 of 37.0 years (95 % confidence interval (CI) 32.8-42.2). We investigated time to EDSS 6 against socioeconomic factors in adolescence. Maternal level of education was significant associated with time to EDSS 6 (p <0.001) (Fig. 3). Only 15 of the 308 who reached EDSS 6 had mothers with a graduate level of education, and the significant results reflect the difference between maternal primary school and secondary school, with a median time to EDSS 6 of 28.0 years (95 % CI 22.7-33.3) and 39.0 years (95 % CI 35.4-42.6) respectively.

The time to EDSS 6 analysis for paternal level of education showed the same pattern as for maternal level of education, but did not reach significance (data not shown). Residency at age 16 and exposure to second-hand smoking were not significantly associated with time to EDSS 6.

3.3. Progression measured by MSSS in 2018

The mean MSSS was 3.39 (range 0.03-9.98, SD 2.56).The results of the linear regression analysis of the association between MSSS and SES at age 16 and at prevalence date, are shown in Table 4. In the univariable linear regression analysis, disease progression is significantly influenced by sex, age at diagnosis, the maternal level of education, disease subtype at diagnosis, second-hand smoking and treatment with DMTs. For the multivariable analysis, we included the variables identified as significant in univariable analysis, as well as all variables

Table 3
Association of socioeconomic factors, treatment and change in EDSS year 0-5 after diagnosis.

	Improvement (reduction of EDSS ≥1 point)	Stable disease (EDSS ±0.5 points)	Moderate progression (increase in EDSS 1-2 points	Marked progression (increase in EDSS ≥2 points)	Total
Mean age 2018, years (SD)	46.5 (11.0)	52.6 (12.2)	55.8 (10.2)	59.7 (10.9)	52.8 (12.1)
p-value					*<.001*
Patient's level of education					
Primary ≤ 9 years (%)	27 (18.5)	38 (13.5)	35 (23.8)	15(18.3)	115 (17.5)
Secondary 10-12 years (%)	51 (34.9)	124 (44.0)	62 (42.2)	33 (53.7)	281 (42.8)
Graduate ≥ 13 years (%)	68 (46.6)	120 (42.6)	50 (34.0)	23 (28.0)	261 (39.7)
p-value			*		*.010*
Centrality of municipality					
Centrality indices 1 and 2 (%)	86 (58.9)	133 (46.7)	68 (45.9)	43 (51.8)	330 (49.8)
Centrality indices 3 and 4 (%)	54 (37.0)	120 (42.1)	69 (46.6)	34 (41.0)	277 (41.8)
Centrality indices 5 and 6 (%)	6 (4.1)	32 (11.2)	11 (7.4)	6 (7.2)	55 (8.3)
p-value					*.076 (n. s.)*
Hospital responsible for follow-up					
University Hospital (%)	26 (20.8)	55 (22.2)	25 (18.4)	13 (18.6)	119 (20.6)
General Hospital (%)	98 (78.4)	193 (77.8)	110 (80.9)	571 (81.4)	458 (79.1)
p-value					*.761 (n. s.)*
Current smoking					
Yes (%)	26 (18.3)	80 (26.6)	44 (30.6)	22 (27.5)	172 (26.6)
No (%)	116 (81.7)	200 (71.4)	100 (69.4)	58 (72.5)	474 (73.4)
p-value					*.081 (n. s.)*
Ever treated with DMT					
Yes (%)	122 (83.6)	194 (68.1)	89 (60.1)	38 (45.8)	443 (66.9)
No (%)	24 (16.4)	91 (31.9)	59 (39.9)	45 (54.2)	219 (33.1)
p-value				*	*<.001*
Mean MSSS score (SD)	2.03 (2.05)	2.73 (2.10)	4.43 (2.44)	6.97 (1.99)	3.45 (2.65)
p-value					*<.001*

EDSS = Expanded Disability Status Scale, SD = standard deviation, n.s. = not significant, DMT = Disease Modifying Treatment, MSSS = Multiple Sclerosis Severity Score
* = significant association at level < 0.05 in posthoc analysis when compared to category "stable disease"

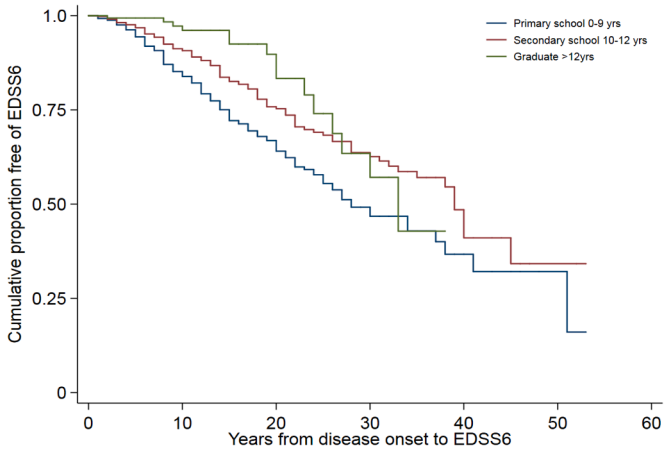

Fig. 3. Kaplan-Meier of time from onset to EDSS 6 against maternal level of education at patient's age 16.

describing conditions from adolescence. Subtype at diagnosis and treatment with DMTs are strongly associated, and to avoid multicollinearity, we only included treatment with DMT ("yes" or "no"). The final model highlights younger age at diagnosis, female sex, DMTs and the patients' level of education as the significantly reducing coefficient for the prediction of MSSS. From adolescence, the only variable significantly included in the final model, is maternal level of education at age 16, but in return, this variable influences MSSS at the same level as DMT. These factors explained 11 % of the variance in MSSS ($R^2 = 0.11$).

We have stratified the study population by the maternal level of education and the results of demographic data are shown in Table 5. The proportion of females is not significantly different in the three groups. Supplementary tables 5b and 5c show the results of demographic data for paternal level of education and residency at age 16.

4. Discussion

This study on the impact of socioeconomic status on disease progression in MS is the first to focus on SES in adolescence. We have used

Table 4
Socio-economic factors associated with MSSS using linear regression analyses.

	Univariable analyses β coefficient (SE)	p-value	Multivariable Model β coefficient (SE)	p-value	Final Model β coefficient (SE)	p-value
Sex						
Female	Ref.					
Male	-0.75 (0.15)	<0.001	-0.73 (0.17)	<0.001	-0.61 (0.16)	<0.001
Maternal level of education *						
Primary ≤ 9 years	Ref.					
Secondary 10-12 years	-0.81 (0.16)	<0.001	-0.53 (0.18)	0.004	-0.49 (0.16)	0.003
Graduate ≥ 13 years	-1.25 (0.22)	<0.001	-0.57 (0.27)	0.04	-0.58 (0.24)	0.015
Paternal level of education*						
Primary ≤ 9 years	Ref.					
Secondary 10-12 years	-0.26 (0.17)	0.13	0.15 (0.19)	0.43		
Graduate ≥ 13 years	-0.80 (0.21)	<0.001	0.11 (0.25)	0.66		
Centrality of municipality*						
Centrality indices 1 and 2	Ref.					
Centrality indices 3 and 4	-0.12(0.17)	0.50	-0.06 (0.16)	0.70		
Centrality indices 5 and 6	-0.16 (0.24)	0.50	-0.12 (0.24)	0.61		
Second-hand smoking						
No	Ref.					
Yes	0.48 (0.16)	0.003	-0.34 (0.17)	0.84		
Age at diagnosis, years	0.06 (0.01)	<0.001	0.04 (0.01)	<0.001	0.040 (0.01)	<0.001
Age in 2018, years	0.06 (0.01)	<0.001	Not included			
Subtype MS at diagnosis			Not included			
RRMS	Ref.					
PPMS	2.50 (0.23)	<0.001				
SPMS	2.73 (0.36)	<0.001				
Hospital responsible for follow-up			Not included			
University Hospital	Ref.					
General Hospital	0.12 (0.18)	0.50				
Disease modifying treatment			Not included			
None	Ref.					
Moderate efficacy DMT	-1.24 (0.17)	<0.001				
High efficacy DMT	-0.40 (0.26)	0.12				
Both moderate and high efficacy DMT	-0.81 (0.19)	<0.001				
DMT, dichotomized						
No	Ref.					
Yes	-0.97 (0.15)	<0.001	-0.52 (0.19)	0.007	-0.49 (0.17)	0.004
Patients own level of education(2018)						
Primary ≤ 9 years	Ref.					
Secondary 10-12 years	-0.49 (0.20)	0.02	-1.00 (0.22)	<0.001	-0.60 (0.21)	0.004
Graduate ≥ 13 years	-1.21 (0.20)	<0.001	-1.31 (0.22)	<0.001	-0.96 (0.21)	<0.001
Current smoking (2018)			Not included			
No	Ref.					
Yes	0.26 (0.16)	0.10				

* = variables at persons age 16.
MSSS = Multiple Sclerosis Severity Score, Ref. = reference value, SE= Standard error of β, RRMS = relapsing remitting multiple sclerosis, PPMS = primary progressive multiple sclerosis, SPMS = secondary progressive multiple sclerosis, DMT=disease modifying treatment

parental levels of education and residency at age 16, and exposure to second-hand smoking as measures of SES in adolescence. Of these factors, the maternal level of education has a significant impact on the patient's disease progression after diagnosis of MS. Maternal level of education beyond secondary school is associated with less pronounced disease progression measured by EDSS and MSSS. The impact of the maternal level of education is similar to the impact of DMTs. The paternal level of education shows the same pattern, but does not reach statistically significance. The place of residency (urban vs rural) at age 16 does not contribute to any of the measures of progression. Factors contributing to increased risk of disease progression are male sex, older age at diagnosis, progressive subtype of MS at diagnosis, exposure to second-hand smoking and primary school as the patient's highest level of educational attainment.

The impact of socioeconomic status in adolescence on disease progression in MS is in accordance with observations in other conditions (Wolfe, 2015; Ben-Shlomo and Kuh, 2002). The overall explanation for the finding of impact of parental level of education is likely complex in MS. People with a chronic illness need the cognitive resources to absorb information and follow recommendations for treatment and lifestyle. Receiving adequate support from close relatives, and having larger available socioeconomic resources are the strongest predictors of self-management in MS (Wilski et al., 2015).

Health-related behaviors are adapted from parents in childhood, and will be reflected in the person's later life (Gunnarsdottir et al., 2017). There is considerable evidence that a variety of symptoms and conditions precede a diagnosis of MS (Disanto et al., 2018; Wijnands et al., 2017), but these studies do not control for socioeconomic status. There is a clear correlation between education and several life-style factors. In this study, we chose the parental level of education as a central variable for the analyses, to compensate for the fact that a diagnosis of MS may influence the person's own educational attainment (Cortese et al., 2016). We did, however, find that our MS population has a similar level of education as the background population, also when the known correlation between parental and individual level of education is taken into account (Weinberg et al., 2019). This might also be seen as a potential selection bias, as our study only included patients who provided written consent. People with a higher level of education are more likely to participate in studies (Reinikainen et al., 2018).

Smoking is a lifestyle factor, as well as a risk factor of MS, which also has a significant impact on outcomes and overall prognosis in MS (Rosso and Chitnis, 2020). However, current smoking was not a significant risk factor for a more pronounced disease progression in our study. A limitation of our study is that we used smoking status in 2018. Hence, many

Table 5
Demographics by subgroups of maternal educational level.

	Maternal education level at age 16			
	Primary school (0-9 years)	Secondary school (10-12 years)	Graduate (>12 years)	p-value
Numbers all	496	684	224	
Numbers female (%)	349 (70.4)	482 (70.5)	162 (72.3)	n.s.
Age onset, mean (SD)	35.7 (10.5)	33.8 (10.1)	31.0 (9.4)	<.001
Time onset-diagnosis in years, mean (SD)	5.7 (6.6)	5.4 (7.3)	3.8 (5.6)	0.004
Age diagnosis, mean (SD)	41.1 (10.9)	39.0 (10.9)	34.7 (9.6)	<0.001
EDSS diagnosis, median (IQR)	2.5 (2.0-3.5)	2.0 (2.0-3.0)	2.0 (1.5-3.0)	<0.001
Proportion RRMS at diagnosis (%)	372 (76.5)	547 (83.8)	200 (94.8)	<0.001
Proportion treated with DMT (%)	286 (57.7)	434 (63.5)	166 (74.1)	<0.001
MSSS 2018, mean (SD)	3.89 (2.66)	3.10 (2.50)	2.63 (2.1)	<0.001
Proportion smoking 2018 (%)	172(35.6)	164 (24.3)	49 (22.8)	<0.001
Centrality of residency at 16 years age (%)				
Centrality indices 1 and 2	113 (35.6)	202 (39.9)	100 (50.3)	
Centrality indices 3 and 4	160 (50.5)	219 (43.3)	84 (42.2)	
Centrality indices 5 and 6	44 (13.9)	85 (16.8)	15 (7.5)	0.001

SD = Standard deviation, IQR=interquartile range, n.s.= not significant, EDSS = Expanded Disability Status Scale, RRMS = Relapsing remitting multiple sclerosis, DMT = Disease Modifying Treatment, MSSS = Multiple Sclerosis Severity Score

of the patients who self-report as non-smokers in 2018 might have been former smokers, and there are data arguing for a dose-response effect of smoking on MS (Wingerchuk, 2012). In Norway, as in most countries, the proportion of daily smokers has decreased in recent years (WHO global report on trends in prevalence of tobacco use 2000-2025 2019). The classification of former smokers in the group of current non-smokers may explain why we did not find the same impact of smoking on disease progression as previous studies (Degelman and Herman, 2017; Chan et al., 2002). The impact of second-hand smoking in adolescence on progression in our data supports the explanation of smoking as an important risk factor. We could also consider including ethnicity and lifestyle factors such as body mass index, nutrition, including level of vitamin D and level of physical in the multivariate analyses. However, these are all known risk factors for developing MS (Wesnes et al., 2015; Abdollahpour et al., 2020; Wesnes et al., 2018; Dobson et al., 2020) and one might argue that these factors are too strongly correlated with SES to be included as independent risk factors in the analysis, and that the level of both patient's and parental education is the most relevant measure.

The impact of the parental level of education cannot be explained by lifestyle factors alone. When dividing the population into groups by the parental educational level, we found that the age at onset, age at diagnosis and time from onset to diagnosis are significantly lower for the patients whose parents had a graduate level of education. Older age at disease onset is associated with poorer prognosis (Guillemin et al., 2017). The significant differences in these important characteristics of MS are shown both for maternal and paternal levels of education. In the subgroup with highly educated parents, the proportion of RRMS is higher and the median EDSS is lower at diagnosis, which we consider an expression of the same phenomenon. In a socioeconomic setting, the explanation may be that parents with a high level of education both pay more attention to symptoms and teach their children more relevant health-related behavior. In addition, they may also encourage early contact with the health care system for diagnostic clarification upon symptom onset, and provide valuable information when differentiating relapsing and primary progressive MS. Thus, the finding of a better disease outcome in patients whose parents had a higher level of education may possibly be reflected in increased awareness and earlier diagnosis of MS. Earlier diagnosis most often leads to earlier treatment initiation, and disease modifying treatment has had an impact on delaying disease progression (Simonsen et al., 2020). In accordance with previous studies (Brown et al., 2019), we found a significantly less pronounced progression for the DMT-treated population. There is evidence that access to the most effective treatment is facilitated by SES (Calocer et al., 2018), but this needs to be further investigated.

It is interesting that when addressing the impact on the different measures of progression, we only found significant impact with the maternal level of education. Numerous studies have, however, shown strong correlations between maternal education and various childhood outcomes, such as health and mortality. Different models have tried to explain this pattern, one of which includes the tendency for highly educated mothers to be older when giving birth and in general having fewer children, with potentially giving more attention to each (Lundborg P and Rooth, 2012). We have not adjusted our data for maternal age and numbers of siblings in our patients and therefore cannot comment further on this hypothesis.

A study from Telemark, one of the counties in our population, documented a higher prevalence of MS in rural versus urban areas in the period from 1999 to 2019 (Flemmen et al., 2020). The level of education is generally higher in urban areas (centrality indices 1 and 2) of Norway, and this may affect the results. However, we did not find any differences in progression in terms of place of residence, neither at 16 years of age, nor at prevalence date. The Norwegian health service aims to provide equal treatment for all patients. All MS patients attend a neurological department and the cost of DMT's are covered by the health care system. The BOT registry comprises patients who live centrally in the capital and are treated at a University hospital, as well as patients who live a 3-4 hours' drive from a neurologist at a general hospital. A potential weakness in our study is that the number of MS patients living in the most central areas (centrality indices 1 and 2) is relatively smaller than in the background population. However, we found no differences in progression depending on hospital responsible for follow-up.

We have used a real-world, population-based cohort with patients diagnosed across a wide time span, living in a geographically well-defined area, but still with large variations in socioeconomic factors. This improves the validity of our results. All data used as measures for socioeconomic status are validated data from Statistics Norway, with the exception of information on smoking status, which was collected through questionnaires. This reduces the potential recall-bias. A recurring question in the search for factors that affect the course of diseases is if the measures obtained at one time reflect the same underlying processes as those obtained at other stages of life. Our population covers a wide time-span, diagnosed from 1943 to 2018. Even though the socioeconomic data are collected from a reliable source (Statistics Norway), the changes over time may affect the analyses, like proportion of smokers and the general level of education (Gakidou E et al., 2010).

Another potential bias is the possibility of misclassification in the registered EDSS. The EDSS at diagnosis may be influenced by an ongoing relapse, and thus possibly underestimating the change in EDSS the first five years. However, we found a similar significance of maternal level of education on time to EDSS 6, where the EDSS at diagnosis is irrelevant. We would argue that this misclassification is likely independent of socioeconomic status and will not have an impact on the results.

In conclusion, when investigating the impact of socioeconomic factors in adolescence on disease progression, we found the maternal level of education at patient's age 16 to be the most important impact factor.

We have demonstrated that the MS patients whose mothers have a higher level of education have a less pronounced disease progression with an impact similar to the impact of DMTs. This can partly be explained by earlier diagnosis and earlier initiation of DMTs. It is important to identify the association between socioeconomic status and disease progression, and the influence of SES on access to relevant treatment needs closer investigation.

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Author statement

Author contributions for paper: Maternal education has significant influence on progression in multiple sclerosis CRediT author statement:

Heidi Øyen Flemmen: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Visualization

Cecilia Smith Simonsen: Conceptualization, Methodology, Software, Validation, Investigation, Data Curation, Writing – Review and editing

Line Broch: Conceptualization, Methodology, Software, Validation, Investigation, Data Curation, Writing – Review and editing

Cathrine Brunborg: Methodology, Formal analysis, Writing – Review and editing

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Data statement

Maternal education has significant influence on progression in multiple sclerosis

Due to the sensitive nature of the variables registered and the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

A limited version of the data can be released upon reasonable request to the corresponding author.

Declaration of Competing Interest

Dr. Flemmen reports grants and personal fees from Biogen and Novartis, personal fees from Sanofi and Merck, grants from Odd Fellow research fund and grants from Ingrid and Fritz Nielsen's legacy during the conduct of the study.

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Dr. Brunborg has nothing to disclose.

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Dr. Moen has nothing to disclose.

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Supplementary materials

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